FLU-INNATE

Innate immunity in influenza virus infection of mammalian airways

SIXTH FRAMEWORK PROGRAMME

EUROPEAN COMMISSION
Community Research

The Project

FLUINNATE www.fluinnate.org

Title: Innate immunity in influenza virus infection of mammalian airways
Acronym: FLUINNATE
Project number: 044161
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Instrument: STREP

Summary

Influenza A viruses are still a major public health problem. They cause a highly contagious respiratory disease in humans and are responsible for periodic epidemics or pandemics, with high mortality rates. The most devastating pandemic occurred in 1918 with millions of deaths worldwide. The avian H5N1 strains currently circulating in birds across Asia and Europe have a high pathogenic potential for humans and are feared to cause the next pandemic if they acquire sufficient human-to-human transmissibility. The molecular mechanisms which determine increased virus virulence in humans are presently not well understood. Influenza viruses enter the human respiratory tract and must replicate in the face of multiple innate immune defence mechanisms to establish infection in vivo. Successful viruses must adapt to intrinsic cellular restriction factors and evolve the capacity of counteracting the antiviral interferon response.

FLUINNATE combines the expertise of leading laboratories in the field. The consortium will identify and characterize the essential viral and host factors that determine the outcome of infection.

The emphasis is on viral replication fitness, host adaptation processes and host defense mechnisms. Human, avian and porcine influenza A viruses will be studied in animal models and in cell culture systems, such as human airway epithelium. FLUINNATE will provide new information which is important for better understanding emerging influenza viruses and for generating efficient control measures against these devastating pathogens.

Participants

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AIM of the Project

The FLUINNATE objectives focus on the identification of influenza A virus genes and gene products which contribute to virulence/pathogenicity in experimental animal and tissue culture models.
The required animals are available and will comprise mice with the wild-type Mx1 gene as part of the full innate immune response, various strains with targeted mutations in specific genes and pigs as natural hosts and “mixing vessels” for influenza A viruses. In addition, human airway and porcine epithelial cell cultures will be established and characterized. Human airway epithelial cell cultures are a rare but most precious substrate to study the biology of influenza virus infection.
The influenza viruses used will be human, avian and swine strains, some of which will be generated by reverse genetics entirely from plasmids. Stock viruses and single and multi-segment reassortants will be produced and fully characterized together with the parental strains with respect to growth kinetics in tissue culture and in vivo, the capacity to induce or respond to interferon, and the capacity to induce disease or death in experimental animals. The technology for expressing, purifying and analyzing the viral RNA polymerase complex will be established and further refined, as well as biochemical and biophysical approaches to identify co-purifying host cellular factors.
Advanced tests for protein-protein interactions such as the yeast three-hybrid system will be set up and candidate interactors evaluated in functional tests, based on transfection experiments.

Potential applications

It is expected that FLUINNATE will provide innovative vistas on the immunopathology of influenza infection as well as candidate new markers and possibly therapeutic agents. Using cutting-edge technology (such as reverse genetics systems) useful recombinant viruses will be produced and provided to the scientific community for research purposes. Results on antiviral host restriction factors and viral virulence determinants will be of great interest to epidemiologists and health care authorities and may have an impact on future pandemic planning.

Publications

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2. **A.S. Gambaryan, A.B. Tuzikov, G.V. Pazynina, J.A. Desheva, N.V. Bovin, M.N. Matrosovich, A.I. Klimov.** 6-sulfo sialyl Lewis X is the common receptor determinant recognized by H5, H6, H7 and H9 influenza viruses of terrestrial poultry. *Virology Journal, 5:85 (2008)*

3. **O. Haller, G. Kochs, P. Staeheli.** Influenza A Virus Virulence and Innate Immunity: Recent Insights from New Mouse Models. *In: "Avian Influenza", pp.134-155, H.-D. Klenk, M.N. Matrosovich, J. Stech (eds): Monogr Virol., Basel, Karger, vol 27, (2008)*

4. **O. Haller, F. Weber.** The Interferon Response Circuit in Antiviral Host Defense. in: Proceeding of the Royal Academy of Medicine in Belgium (KAGB), Erik de Clercq, *ed. (in press)*

5. **M.N. Matrosovich, A.S. Gambaryan, H.-D. Klenk.** Receptor specificity of influenza viruses and its alteration during interspecies transmission. *In: "Avian Influenza", pp.134-155, H.-D. Klenk, M.N. Matrosovich, J. Stech (eds): Monogr Virol., Basel, Karger, vol 27, (2008)*

6. **N. Naffakh, A. Tomoiu, M.A. Rameix-Welti, S. van der werf.** 2008. Host restriction of avian influenza viruses at the level of the ribonucleoproteins. *Annual Review of Microbiology, 62: 403-24 (2008)*

7. **P.C. Reading, S. Bozza, B. Gilberston, M. Tate, S. Moretti, E.R. Job, E.C. Crouch, A.G. Brooks, L.E. Brown, B. Bottazzi, L. Romani, A. Mantovani.** Antiviral activity of the long chain Pentraxin 3 against influenza viruses. *J. Immunol., 180:3391-3398 (2008)*

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